Attorney Docket No. Enz-53(C)

REMARKS

Claims 246-253, 255-262 and 264-270 are pending in the above-referenced application. Claims 253, 256 and 261-262 have been canceled without prejudice. Applicants reserve the right to file subsequent continuation and/or divisional application claiming the canceled subject matter.

Claim 246 has been amended to more distinctly claim that which Applicant regards the invention. The subject matter of claim 256 has been incorporated into amended claim 246. Amended claim 246 is supported by the specification on pages 31-47. For example, on page 34, lines 4-11 and 13-16 states

> The present invention is a defined chemically modified nucleic acid construct (CHENAC) which, upon introduction into a cell, is capable of biological, i.e., production of a protein in a cell or interaction with a nucleic acid or protein in a cell. The said chemical modification directly or indirectly renders the construct capable of one or more of the following properties: a) binding to a target cell b) nuclease resistance c) providing a mechanism for introduction of the nucleic acid into cells d) providing nuclease resistance within the cytoplasm e) facilitating transfer of the nucleic acid from the cytoplasm to the nucleus f) providing a longer lifetime within the cell g) providing a signal for integration into cellular DNA. In the present invention, one or more of the above properties is capable of being provided without substantially interfering with the biological function of said nucleic acid. The present invention uses chemical modification of nucleic acid to attach directly or indirectly one or more ligands tor chemical modifications or other moieties to a nucleic acid construct.

Furthermore, page 39, lines 9-14 recite:

> Ligands or chemical modifications can be attached to the nucleic acid, modified nucleic acid or nucleic acid analogue by modification of the sugar, base and phosphate moieties of the constituent nucleotides (reference omitted) or to a non nucleic acid segment of the CHENAC such as

> polysaccharide, polypeptide and other polymers both natural and synthetic.

Furthermore, claims 249, 259, 264-268 and 270 have been amended to more distinctly claim that which Applicants regard as their invention. As will be discussed in further detail below, claims 249, 264, 265 and 270 have been amended in order to address the rejections under 35 U.S.C. §112, second paragraph. Claim 266 has been amended to recite that the" construct **carries** a net positive charge.....". Claim 267 has been amended in view of the amendment of claim 246 and recites that the construct comprises unmodified nucleotides and one or more nucleotide analogs. Claim 268 has been amended to specifically recite "A **nucleic acid** construct" and to recite that the construct is **bound covalently** to an entity comprising a ligand in two or more locations on said construct. Amended claim 268 is supported by the specification on page 40. For example , page 40, lines 10-16:

> In a further embodiment the present invention provides the construct, described bove, further comprising at least one ligand attached covalently or noncovalently to one or more of the modified nucleotide analogs, nonnucleic acid entities (or combinations of the foregoing). Such ligands and chemical modifications can be added directly to the CHENAC through covalent and non-covalent interactions. Covalent additions can be made by chemical methods (citation omitted) and enzymatic incorporation.

No new matter has been added to the amended claims. Furthermore, as discussed above, the amended claims are supported by the specification.

1. **The Objection to Claim 256**

Claim 256 is objected to because of the following informalities: the phrase "both strand" is grammatically incorrect, and should be amended to read "both strands", if such is the intended recitation. Appropriate correction is required.

Attorney Docket No. Enz-53(C)

In response, claim 256 has been canceled. The subject matter of claim 256 is incorporated into amended claim 246. Therefore, the objection has been overcome and should be withdrawn.

2. The Rejection Under 35 USC §112, Second Paragraph

The Office Action specifically states with respect to claims 249, 256, 261, 264, 265 and 270:

> Claim 249 recites the limitation "said sequence segment" in claim 248. There is insufficient antecedent basis for this limitation in the claim.
>
> Claim 256 recites the limitation "said sequence segment" in claim 246. There is insufficient antecedent basis for this limitation in the claim.
>
> Claims 261, and by dependency claim 262, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 261 requires the claimed construct to exhibit a "further biological activity", whereas no upstream activity for the claimed construct has yet been delineated.
>
> Claim 264 recites the limitation "said ligand..." in claim 246. There is insufficient antecedent basis for this limitation in the claim. The remainder of this action presumes the dependency to be directed to claim 257, which is the only earlier claim that recites any type of ligand.
>
> Claim 265 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 265 refers to "the construct of claim 263". However, claim 263 has been canceled. The remainder of this action presumes the dependency to be directed to claim 257, which is the only earlier claim which recites any type of ligand.
>
> Claim 270 recites the limitation "said polynucleotide tale" in the construct of claim 248.
>
> There is insufficient antecedent basis for this limitation in the claim. It is presumed for the remainder of this action that the claim in tens to refer to the construct of claim 269,

> which is the immediately preceding claim that recites a polynucleotide tail.

In response, claim 249 has been amended to recite that the **construct** is in double stranded form. Claims 256 and 261 have been canceled. Claims 264 and 265 now depend from claim 257. Claim 270 now depends from claim 268.

In view of the amendments of claims 249, 264, 265 and 270, and cancellation of claims 256 and 261, Applicants assert that the rejections under 35 USC §112, second paragraph have been overcome. Therefore, Applicants respectfully request that the rejections under 35 USC §112, second paragraph be withdrawn.

3. The Rejections Under 35 USC §112, First Paragraph

Claim 268 has been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Office Action specifically states:

> Claim 268 is drawn to a construct which when present in a cell produces a nucleic acid product, said construct being bound non-ionically to an entity comprising a chemical modification or a ligand in two or more locations on said construct.
>
> It is not clear from a review of the specification as filed that the specification provides adequate support for the phrase "in two or more locations on said construct". Applicants arguments suggest only that all amendments are broadly supported by the disclosure as filed, and does not indicate with any specificity were any support for any such amendments might be. Furthermore, while the specification broadly discusses chemical modifications of nucleic acid constructs, it is not clear where specific support might be had for a recitation of "two or more locations" within the context of the claimed invention. Should applicants disagree, applicants are invited to point out with specificity by page and line number where any such support may exist.

Applicants respectfully traverse the rejection. Applicants first note that claim 268 has been amended to recite that the construct is covalently bound to an entity comprising a ligand in two or more locations. It is Applicants' assertion that there is indeed support for claim 268. Specific illustrations are provided, for example, in Figures 1-3 and are described in Examples 1-4. Clearly all of these figures depict the presence of chemical modification or ligand in two or more locations on the construct.

In view of the above arguments, Applicants assert that the rejection of claim 268 under 35 USC §112, first paragraph (written description) have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

4. The Rejections Under 35 USC §102

Claims 246-253, 255-262, and 264-270 are rejected under 35 U.S.C. 102(a) as being anticipated by Overell et al. (WO 95/28494, applicants IDS of 7 February 2005) and by Vos et al. Each of the rejections are discussed below.

4.1 Overell

The Office Action specifically asserts:

> Overell et al. teach a gene delivery fusion protein construct which bind to vectors to enhance transduction efficiency. Thus, Overell et al. teach a chemically modified nucleic acid construct, which is the vector bound to a fusion protein which is a non-nucleic acid entity, wherein said construct directs the synthesis of a nucleic acid product having a biological activity, wherein said product is chosen from sense RNA, that is circular, or that is double stranded, and that has a terminus which comprises a polynucleotide tail, which may be hybridized to a complementary polynucleotide sequence, and wherein the construct comprises DNA. Overell et al. also teaches wherein said non-nucleic acid entity is attached to a single strand or double strand and to a natural or synthetic polymer, which

> is a polypeptide, which is a heteropolymer. Overell et al. is considered to teach the limitations of claims 264 and 265 because these claims do not limit the nucleic acid entity for reasons provided above. Overell et al. is considered to teach that said construct is hydrophobic, or wherein said construct comprises unmodified nucleotides one non-nucleic acid entity, and wherein said construct produces a nucleic acid product, and said construct is considered to be bound non-ionically to an entity comprising a chemical modification in two or more locations on said construct. Finally, Overell et al. is considered to teach such constructs which comprise a polynucleotide tail which may also be hybridized to a complementary polynucleotide sequence.

Applicants respectfully traverse the rejection. Every element and limitation of a claimed invention must be found in a single prior art reference and arranged as in the claim for anticipation to preclude patent protection in view of 35 USC §102. *Brown v. 3M*, 265 F.3d 1349 (Fed. Cir. 2001). It is Applicants position that the pending claims do not contain each and every element of the Overell et al. disclosure . Specfically, Applicants respectfully disagree with Examiner's position that binding of a protein via electrostatic forces to a nucleic acid results in a "chemically modified nucleic acid" since no chemical reactions are involved. Furthermore, Overell et al. discloses a complex between a fusogenic protein and a non-modified nucleic acid sequence. There is no disclosure in Overell et al. that the nucleic acid sequence comprises a modified nucleotide or a nucleotide analog.

However, in order to advance prosecution, Applicants note that claim 246 has been amended to recite that the **chemically modified nucleic acid construct** contains a modified nucleotide or nucleotide analog which contains a non-nucleic acid entity. In contrast, Overell discloses a complex **not** a construct. The complex comprises a nucleic acid and a fusogenic protein (a non-nucleic acid entity). Furthermore, the nucleic acid disclosed in Overell et al. does not contain a modified nucleotide or nucleic acid analog.

It is Applicants position that claims 247-252, 255, 257-260, 264-267 are not anticipated by Overell et al. since they are dependent claims. Specifically, claims 247,

248, 246, 252, 255, 257, 266-267 depend from claim 246; claims 249-250 depend from claim 248; claim 251 depends from claim 250; claims 258, 264 and 265 depends from claim 257; claim 260 depends from claim 259. Therefore, arguments made in connection with claim 246 would be applicable to these dependent claims as well.

Amended claim 268 would not be anticipated by Overell et al. As noted above, Overell et al. discloses a complex between a fusogenic protein and a nucleic acid sequence. In Overell et al., a fusogenic protein is complexed to the nucleic acid sequence; a fusogenic protein is not a ligand. In contrast, amended claim 268 recites that the construct is bound **covalently** to an entity comprising a ligand in two or more locations on the construct. Therefore, claim 268 would not be anticipated by Overell et al. Claims 269 and 270 depend from claim 268 and would also thus not be anticipated by Overell et al.

In view of the above arguments and the amendments of claims 246 and 268, Applicants assert that the rejection over Overell et al. under 35 USC §102 has been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

4.2 Vos et al.

Claims 246-253, 255-262, and 264-270 are rejected under 35 U.S.C. 102(b) as being anticipated by Vos et al. (Mol. Cell. Biol. 1989, 9(7) 2897-2905). The Office Action specifically states:

> Vos et al. teaches a plasmid which has been chemically cross-linked with HMT. Vos et al. teaches that HMT cross-links the plasmid which enhances its chromosomal integration efficiency. Vos et al. is thus considered to teach a chemically modified nucleic acid construct, which is the cross-linked vector which Vos comprises modified nucleotides, wherein said construct integrates into the chromosome and thus directs the synthesis of a nucleic acid product having a biological activity, wherein said product is chosen from DNA, that is circular, and that is

> double stranded, and that has a terminus which comprises a polynucleotide tail, which may be hybridized to a complementary polynucleotide sequence. Vos et al. also teaches wherein said modified nucleotide is attached to a single strand or both strands which is a natural or synthetic polymer, which is a cross-linked plasmid, which is a heteropolymer. Vos et al. is considered to teach the limitations of claims 255-260, 264 and 265 because these claims do not limit the modified nucleotide for reasons provided above. Vos et al. is considered to teach that said construct has an overall net positive or negative charge or is hydrophobic, and wherein said construct comprises unmodified nucleotides and at least one nucleotide analog, and wherein said construct produces a nucleic acid product which is the chromosome, and wherein said construct is considered to be bound non-ionically to an entity comprising a chemical modification in two or more locations on said construct. Finally, Vos et al. is considered to teach such constructs which comprise a polynucleotide tail which may also be hybridized to a complementary polynucleotide sequence.

Applicants respectfully traverse the rejection. As noted above, Vos et al. disclose psoralen modification of a plasmid. Therefore, Vos does disclose a nucleic acid construct which comprises a modified nucleotide; the modification is the psoralen crosslinking. However. In contrast to subject matter recited in claim 246, Vos fails to disclose a non-nucleic acid entity attached to the modified nucleotide. There is no indication or even speculation in Vos that psoralen modification of DNA results in nuclease resistance, cell targeting, cellular localization or nuclear localization. Although Vos does describe enhancement of chromosomal integration this is an event that would take place after nuclear localization has already occurred. No evidence is presented for enhancement of transportation of the modified nucleic acid from the cytoplasm into the nucleus. Vos actually states on page 2903, col.1, 3rd paragraph:

> Our main conclusion is that bulky lesions such as pyrimidine dimmers and psoralen adducts stimulate integration of plasmid DNA into chromosomes. Several arguments excule the possibility that a step preceding integration is the target for the enhanced transformation.

It is Applicants position that claims 247-252, 255, 257-260, 264-267 are not anticipated by Vos et al. since they are dependent claims. Specifically, claims 247, 248, 252, 255, 257 and 266-267 depend from claim 246; claims 249-250 depend from claim 248; claim 251 depends from claim 250; claims 258, 264 and 265 depends from claim 257 and claim 260 depends from claim 259. Therefore, argument made in connection with claim 246 would be applicable to these dependent claims as well.

Claim 268, as amended, would not be anticipated by Vos et al. Specifically, claim 268 has been amended to more distinctly claim that which Applicants regard as their invention and to advance prosecution. It is not acquiescence to the Examiner's position. Applicants reserve the right to file subsequent continuation and/or divisional applications on canceled subject matter. The construct recited in amended claim 268 is bound to an entity comprising a ligand in two or more locations. In contrast, the plasmid of Vos is not bound to such an entity. Claims 269 and 270 would not be anticipated by Vos since it depends from claim 268.

In view of the amendments of claims 246 and 268 and the above arguments, Applicants assert that the rejection under 35 USC §102 has been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

SUMMARY AND CONCLUSIONS

Claims 246-253, 255-262 and 264-270 are pending in the above-referenced application. Claims 253, 256 and 261-262 have been canceled without prejudice.

Attorney Docket No. Enz-53(C)

Claims 246, 249, 259, 264-268 and 270 have been amended to more distinctly claim that which Applicants regard as their invention.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at (914) 712-0093.

Respectfully submitted,

Cheryl H. Agris

Cheryl H. Agris, Reg. No. 34,086

ENZO LIFE SCIENCES, INC.
c/o ENZO BIOCHEM, INC.
527 Madison Avenue, 9th Floor
New York, New York 10022